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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,050	05/17/2001	Hidetoshi Uemura	UEMURA 8	4088

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,050	UEMURA ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 12-30* is/are pending in the application.

4a) Of the above claim(s) *19,21-24,26,28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,12-18,20,25,27,30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Invitrogen

DETAILED ACTION

Status of the Application

Claims 1-6, 12-30 are pending.

Applicant's amendment of claims 1-6, 13-18, 20, 25, 27, addition of claim 30, submission of a new abstract, and amendments to the specification in a communication filed on 1/30/2004 are acknowledged.

New claim 30 is directed to the elected invention and will be examined with claims 1-6, 12-18, 20, 25 and 27. As indicated in a previous Office Action mailed on 11/4/2003, claims 19, 21-24, 26, 28-29 were withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to an invention non-elected without traverse in Paper No. 12, filed on 8/20/2003. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

1. Claim 6 is objected to due to the recitation of "wherein the polynucleotide....is composed of at least a nucleotide sequence encoding amino acids 36-40 of SEQ ID NO: 19...". For clarity and consistency, it is suggested that the term be amended to recite "wherein the polynucleotide....comprises at least amino acids 36-40 of SEQ ID NO: 19..." or similar. Appropriate correction is required.

2. Claims 20 and 27 are objected to due to the recitation of "fusion protein comprising an amino acid sequence of a target protein..". For clarity and consistency, it is suggested that the term be amended to recite "fusion protein comprising a target protein..". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-6, 12-18, 20, 25, 27, 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 1 (claims 2-6, 12-18, 20, 25, 27, 30 dependent thereon) is indefinite in the recitation of "(c) a nucleotide sequence encoding an amino acid sequence comprising amino acid residues 36-40 of SEQ ID NO: 19 ...., which is cleavable by an enterokinase.." for the following reasons. As written, it is unclear as to what is cleavable by an enterokinase, i.e. amino acids 36-40 of SEQ ID NO: 19 or the polypeptide encoded by the nucleotide sequence of (c). To avoid confusion, it is suggested that the term be replaced with "(c) a nucleotide sequence encoding a polypeptide comprising amino acid residues 36-40 of SEQ ID NO: 19 ...., wherein said polypeptide is cleavable by an enterokinase..". For examination purposes, the term will be interpreted using the suggested language. Correction is required.

6. Claim 1 (claims 2-6, 12-18, 20, 25, 27, 30 dependent thereon) is indefinite in the recitation of "(d) a cloning site into which a nucleotide sequence encoding a target protein can be inserted..." for the following reasons. As indicated in the previous Office Action, a sequence is just a graphical representation of the order in which residues are arranged in a molecule, and what is inserted in an expression vector is a nucleic acid. For examination purposes, the term will be interpreted as "(d) a cloning site into which a polynucleotide encoding a target protein can be inserted...". Correction is required.

7. Claim 2 (claims 13-18, 20, 25, 27 dependent thereon) is indefinite in the recitation of "wherein a nucleotide sequence encoding a target protein is inserted..." for the reasons indicated above regarding claim 1 and the recitation of item (d). It is suggested that the term be amended to recite "wherein a

polynucleotide encoding a target protein is inserted...". For examination purposes, the term will be interpreted using the suggested language. Correction is required. It is noted that if the suggested language is used, claims dependent upon claim 2 may need to be amended accordingly to maintain the proper antecedent basis.

8. Claim 3 is indefinite in the recitation of "wherein the cloning site or the nucleotide sequence encoding the target protein is present successively at the 3' end of the (c)" for the reasons indicated above regarding claim 1 (d) and 2. It is suggested that the term be amended to recite "wherein the cloning site or the polynucleotide encoding the target protein is present successively at the 3' end of (c)". For examination purposes, the term will be interpreted using the suggested language. Correction is required.

9. Claim 4 is indefinite in the recitation of "wherein said polynucleotide is located between the 3'...of the nucleotide sequence encoding the IgG....and the 5' end of the nucleotide sequence (c)" since it is unclear as to how a nucleic acid can be located between sequences. It is suggested that the term be amended to recite "wherein said polynucleotide is located between the 3'end of the polynucleotide encoding the IgG... ....and the 5' end of the polynucleotide having the nucleotide sequence of (c)". For examination purposes, the term will be interpreted using the suggested language. Correction is required.

10. Claim 5 is indefinite in the recitation of "wherein the polynucleotide encoding at least one amino acid residue is a nucleotide sequence encoding an amino acid sequence comprising..." as it is unclear how a nucleic acid can be a sequence. It is suggested that term be amended to recite "wherein the polynucleotide encoding at least one amino acid residue is a polynucleotide encoding a polypeptide comprising amino acid residues...". For examination purposes, the term will be interpreted using the suggested language. Correction is required.

Claim Rejections - 35 USC § 102

11. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

12. Claims 1-4, 6, 14, 18, 20, 25, 27 were rejected under 35 U.S.C. 102(b) as being anticipated by the New England Biolabs 1995 catalog. This rejection has been discussed at length in Paper No. 13, mailed on 11/4/2003.

13. Amended claims 1-4, 14, 18, 20, 25, 27 are directed to (1) an expression vector comprising a polynucleotide encoding an IgG (k) or a trypsin signal peptide, a polynucleotide encoding a histidine tag, a polynucleotide encoding a polypeptide comprising amino acid residues 36-40 of SEQ ID NO: 19, and a cloning site, (2) a host cell comprising said vector, or (3) a method to produce a target protein or a fusion protein comprising the target protein by cultivating a host cell comprising said vector. The New England Biolabs 1995 catalog does not teach (1) a vector comprising polynucleotide encoding an IgG (k) or a trypsin signal peptide, a polynucleotide encoding a histidine tag, a polynucleotide encoding a polypeptide comprising amino acid residues 36-40 of SEQ ID NO: 19, and a cloning site, (2) a host cell comprising said vector, or (3) a method to produce a target protein or a fusion protein comprising the target protein by cultivating a host cell comprising said vector. Thus, this rejection is hereby withdrawn.

Claim Rejections - 35 USC § 103

14. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

15. Claims 1-4, 12, 14-16, 18, 20, 25, 27, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Invitrogen 1998 product catalog. The Invitrogen 1997 catalog teaches the pRSET A, B, C vectors for prokaryotic expression of proteins (page 37), host cells comprising the vectors and pRSET A. B, C vectors comprising a recombinant protein as a positive expression control (page 37,

Contents and Storage). These vectors all comprise the nucleotide sequence encoding the enterokinase cleavage site (page 37, Description) which contains the peptide DDDK (page 12, right column, Description). pRSET A, B, C also contain a polynucleotide sequence encoding a polyhistidine tag (His6). The cloning site in pRSET A, B, C (i.e. MCS) is immediately after the polynucleotide encoding the enterokinase cleavage site, and the polynucleotide encoding the enterokinase cleavage site is immediately after the polynucleotide encoding His6. pRSET A, B, C do not have a polynucleotide encoding an IgG (k) or a trypsin signal peptide. A target protein produced using the pRSET vectors would be a recombinant fusion protein until enterokinase is used to cleave the His6 tag. In addition, the Invitrogen 1997 catalog teaches the pSecTag2 vectors for expression in mammalian cells. psecTag2 vectors comprise a polynucleotide encoding the mouse IgG(k) secretion signal, a cloning site, a polynucleotide encoding the C-terminal c-myc epitope for detection with the anti-myc antibody, and a polynucleotide encoding a His6 tag (page 46, left column, Description).

Claims 1, 3, and 4 are directed in part to an expression vector comprising a nucleotide sequence encoding an IgG(k) or a trypsin secretory signal peptide, a nucleotide sequence encoding a polyhistidine tag, a nucleotide sequence encoding a polypeptide comprising amino acids 36-40 of SEQ ID NO: 19 (DDDDK), and a cloning site into which a polynucleotide encoding a target protein can be inserted. Claim 2 adds the limitation that a polynucleotide encoding a target protein is inserted in the cloning site. Claim 12 adds the limitation that the expression vector of claim 1 further comprises a polynucleotide encoding an antibody recognition epitope. Claim 14-16 are directed to host cells comprising the expression vector of claim 2. Claim 30 is directed to host cells comprising the expression vector of claim 1. Claims 18, 20, 25 and 27 are directed in part to a method for producing a fusion protein comprising the target protein in host cells transformed with the expression vector of claim 2.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to (1) make an expression vector wherein said vector comprises a nucleotide sequence encoding an

IgG(k) or a trypsin secretory signal peptide, a nucleotide sequence encoding a polyhistidine tag, a nucleotide sequence encoding a polypeptide comprising amino acids 36-40 of SEQ ID NO: 19 (DDDDK; enterokinase cleavage site), and a cloning site into which a polynucleotide encoding a target protein is inserted, (2) make an expression vector as described in (1) further comprising a nucleotide sequence encoding an antibody recognition epitope, (3) transform a host cell with the vectors described in (1) or (2), and (4) make a recombinant fusion protein comprising a target protein by cultivating the host cells of (3) in view of the teachings of the Invitrogen 1997 Catalog..

A person of ordinary skill in the art is motivated to modify the prSET vector such that the IgG(k) secretion signal and the c-myc epitope of the pSecTag vector are added for the benefit of creating an expression vector which allows for secretion of the desired protein and an additional purification tag. Furthermore, a person of ordinary skill in the art is motivated to add the pRSET's polynucleotide encoding the enterokinase cleavage site to the pSecTag vector next to the His6 tag for the benefit of being able to cleave the His6 tag from the target protein after purification. In addition, a person of ordinary skill in the art is motivated to place the polynucleotide encoding the His6 tag prior to the cloning site as the His6 tag may affect the folding/activity of the protein of interest depending on whether the His6 tag is at the C or N terminus. Also, a person of ordinary skill in the art is motivated to transform host cells with said vectors to produce a recombinant fusion protein comprising the target protein which is easier to purify as it would be secreted to the medium and could be further purified/identified with an anti-myc antibody. The benefits of secreting a recombinant protein are well known in the art as secretion to the extracellular medium avoids additional steps in the isolation and purification of the desired protein. The benefits of adding an additional purification/identification tag are well known in the art as additional tags would allow for additional flexibility in the purification process and possibly additional purity.

One of ordinary skill in the art has a reasonable expectation of success at modifying the pRSET vector to include a polynucleotide encoding the IgG(k) secretion signal of the pSecTag vector or modify

the pSecTag vector such that the His6 tag is placed on the N-terminus of the desired protein and to an enterokinase cleavage site next to the His6 tag, since the Invitrogen 1997 catalog teaches expression vectors comprising all the required elements, i.e. IgG(k) secretion signal, His6 tag, enterokinase cleavage site, and cloning site. Furthermore, the molecular biology techniques required to place the required elements in the order recited are well known in the art. One of skill in the art has a reasonable expectation of success at transforming a host cell with the vectors of the Invitrogen 1997 catalog and producing recombinant fusion proteins such as proteins comprising histidine tags, since transformation of host cells with vectors and production of recombinant proteins with such host cells is well known and widely used in the art. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Double Patenting

16. Applicant is advised that should claims 18 and 20 be found allowable, claims 25 and 27 will be objected to under 37 CFR 1.75 as being substantial duplicates thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Since claim 14 is directed to a host cell transformed with the vector of claim 2, claims 25 and 27 both require cultivating the same host cell as that of claims 18 and 20, respectively.

Conclusion

17. No claim is in condition for allowance.

18. Applicant's amendment of claims 1-6, 13-18, 20, 25, 27 and addition of claim 30 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE**

FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

20. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or

relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
April 14, 2004

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